SUMMARY MINUTES

OF THE

CIRCULATORY SYSTEM DEVICES

ADVISORY PANEL MEETING

OPEN SESSION

September 10-11, 2001

Gaithersburg Marriott Washingtonian Center
9751 Washingtonian Boulevard
Gaithersburg, MD

CIRCULATORY SYSTEM DEVICES ADVISORY PANEL MEETING

September 10-11, 2001

ROSTER

Cynthia M. Tracy, M.D. (Voting Chair, September 10 only)
Georgetown University Hospital, Washington, DC

Salim Aziz, M.D. (Voting Member September 10 and 11)
University of Colorado Health Sciences Center, Denver, CO

Warren Laskey, M.D. (Voting Member on September 10, Acting Chair on September 11)
University of Maryland School of Medicine, Baltimore, MD

Janet Wittes, Ph.D. (Voting Member, September 10 and 11)
Statistics Collaborative, Inc.
Washington, DC

Robert Dacey (Consumer Representative, September 10 and 11)
Longmont, CO

Michael Morton (Industry Representative, September 10 and 11)
W.L. Gore and Associates, Flagstaff, AZ

Michael D. Crittenden (Consultant, September 10 and 11)
West Roxbury VA Medical Center, West Roxbury, MA

Thomas Ferguson, M.D. (Consultant, September 11 only)
Washington University School of Medicine, St. Louis, MO

Richard Hopkins, M.D. (Consultant, September 10 only)
Brown University School of Medicine, Providence, RI

Nancy McDaniel, M.D. (Consultant, September 10 only)
University of Virginia, Charlottesville, VA

David Skorton, M.D. (Consultant, September 10 only)
University of Iowa, Iowa City, IA

Chris White, M.D. (Consultant, September 10 only)
Ochsner Clinic, New Orleans, LA

Roberta Williams, M.D. (Consultant, September 10 only)
Keck University of Southern California, School of Medicine, Los Angeles, CA

Kenneth Zakha, Ph.D. (Consultant, September 10 only)
Case Western University, Cleveland, OH

FOOD AND DRUG ADMINISTRATION

Megan Moynahan, M.S.
Panel Executive Secretary

James E. Dillard III
Director, Division of Cardiovascular and Respiratory Devices

Donna Buckley
FDA Reviewer

John E. Stuhlmuller, M.D.
FDA Reviewer

Lisa Kennell
FDA Reviewer

OPEN SESSION—September 10, 2001

Call to Order

Acting Chair Cynthia M. Tracy, M.D., called the meeting to order at 9:10 a.m. and read the charge to the panel, which was to consider a premarket approval application (PMA) for AGA Medical's Amplatzer Septal Occluder and Delivery System, a transcatheter septal closure device for occlusion of secundum atrial septal defects and fenestrations following fontan operation. **Panel Executive Secretary Megan Moynahan** read the conflict of interest statement, noting that an institutional waiver had been granted to David J. Skorton for an interest in a firm potentially affected by the day's deliberations. She also read appointments to temporary voting status for Michael D. Crittenden, Nancy L. McDaniel, Roberta G. Williams, and Richard A. Hopkins. **Dr. Tracy** asked the panel members to introduce themselves and state their areas of expertise.

Open Public Hearing

There were no requests to address the panel. **Ms. Moynahan** stated that the FDA had received eight letters in support of approving the device, all on behalf of the same patient. She summarized a letter from that patient, who related a positive experience upon receiving the device and asked the panel to approve the device.

Sponsor Presentation—PMA P000039 for AGA Medical's Amplatzer Septal Occluder and Delivery System

Mr. Franck Gougeon, Executive Vice President for AGA Medical, introduced the sponsor presentation and read the proposed indications for device use. He described the device and its deployment sequence and explained modifications to the

investigational plan made because of a previous panel recommendation of a nonrandomized trial.

Dr. John P. Cheatham of the Nemours Cardiac Center in Orlando gave a history of atrial septal defect (ASD) closure, explaining the need for closure and the complications involved in surgical ASD closure, which has served as the "gold standard." He listed possible advantages of transcatheter versus surgical therapy, outlining the history of ASD device closure and problems associated with early device designs, and then showed a brief presentation of device insertion.

Dr. Ziyad M. Hijazi, M.D., of the University of Chicago Children's Hospital, described the ASD study, noting its use of an independent statistician, echo core lab, and data safety monitoring board. He explained the definitions used for technical and procedural success, primary efficacy success, and composite success and defined the efficacy endpoint, primary efficacy criterion, and safety criteria. After reviewing the inclusion and exclusion criteria for device and for surgery, he looked at the patient population of 442 device patients and 154 surgical control patients. The major difference between the groups was that the surgical group was lower in age, and the device group had problems associated with older patients. Dr. Hijazi looked at efficacy results in terms of technical success, technical failures, and procedural success, concluding that the primary efficacy results of no significant residual shunt at the 12-month follow-up was achieved by 98.5% of device patients. This rate was statistically equivalent to the surgical group according to the protocol requirements.

Dr. Hijazi discussed the definitions developed by the independent Data Safety Monitoring Board for major and minor complications and presented data on both,

showing that the device's major complication rate was lower than the maximum rate specified by protocol and the overall complication rate was significantly lower for the device than for control. There were no device-related deaths, and the device group had significantly lower procedure time and shorter hospital stay. For the 12-month composite success, the FDA required all attempted patients to be without a major complication, embolization, technical failure or significant shunt at any time and did not allow patients to revert to a success over time, which Dr. Hijazi saw as a conservative definition.

Dr. John W. Moore of St. Christopher's Children's Hospital in Philadelphia summarized the fenestrated fontan study. He explained the background of the procedure, its aims, and the steps involved, and showed a brief video. The study was organized as a single-arm, multicenter registry that used an independent data safety monitoring board and an independent statistician. Efficacy was defined a successful closure of the fenestration at 12 months with a shunt of 2.0 mm or less as shown by Doppler echocardiography. Safety for the device was defined as absence of death and/or major complication rates within defined limits. Dr. Moore listed inclusion and exclusion criteria and explained the study demographics, noting that these patients were slightly younger than the ASD patients, with a predominance of males. Of the total 48 attempted patients, there were two technical failures, both related to anatomical conditions. The primary efficacy result was 100%. Safety results showed a 4.2% rate of major and minor complications, which was within the protocol-defined limits. There were no device-related deaths. Dr. Moore stated that the fenestrated fontan hospital stay was very short and that the procedure's short stay and avoidance of repeated open-heart surgery demonstrated the device's clinical utility.

In conclusion, **Dr. Hijazi** stated that the sponsor had worked with the FDA and the panel to produce a sound clinical study that demonstrated safety and efficacy for both indications.

FDA Presentation

Donna Buckley, lead FDA reviewer, introduced the FDA review team and described the device's features. She stated that the nonclinical evaluation consisted of in vitro, biocompatibility, and in vivo (animal) testing. Ms. Buckley reported that the results of the preclinical testing demonstrated the integrity and functionality of the device for its intended use, and there were no outstanding nonclinical issues.

John Stuhlmuller, M.D., gave an overview of the clinical evaluation. He listed the five clinical data sets: a pivotal cohort of 459 ASD patients, a pivotal cohort of 51 fenestrated fontan patients, and two non-pivotal data sets. The ASD patients were enrolled in a non-randomized, open-label multicenter registry and were compared to prospectively and retrospectively identified surgical control patients who were also enrolled in a non-randomized open-label multicenter registry. All patients completed a prospective one-year follow-up, at which outcome was assessed using a composite clinical success endpoint incorporating aspects of safety and effectiveness, which Dr. Stuhlmuller detailed. He presented statistics on technical success, procedure success, six-month closure, and 12-month closure (as defined in the protocol), all of which showed high success rates for the device. Twelve-month composite clinical success, defined as all patients attempted without major complications, embolization, technical failure, and presence of a significant residual shunt, was achieved by 85.9% of device patients and

94.8 % of surgical patients. Safety results favored the device over the surgical group in terms of major, minor, and overall complications.

For the fenestrated fontan cohort, patients were enrolled in a prospective, open-label, single-arm registry without a control group. Outcome assessment at 12 months was based on effectiveness, defined by successful closure, and safety, defined by lack of adverse events. Of the 48 patients, 46 were implanted. Successful closure was demonstrated in 32 of the 32 patients evaluated at 12 months. Adverse events were evaluated in the 48 patients in which placement was attempted, with a total of four adverse events (two major and two minor).

Open Committee Discussion

Donna Buckley read the FDA questions for panel review. **Lead panel reviewer Roberta Williams, M.D.**, asked for additional information from sponsors on sensitivity to thrombus, possible alternatives to transesophageal echocardiography for device implantation, the postoperative prohibition on serious activity, and possible phrenic damage. Other members of the panel asked about possible use of the device with patients allergic to nickel, exclusion criteria, and the different patient populations used in device and control groups, in particular whether the age difference between the groups produced clinically significant differences in result. Statistical concerns involved the age distribution of the data sets and the adjusted efficacy rate when there are people in both age groups for device and control. The lack of follow-up data was a panel issue, as was the lack of information on the five failures listed. A number of members raised concerns about whether the surgical procedure used was a fair control because it was no longer standard operating procedure and about the use of the retrospective surgical data.

Other issues included whether the device is completely endothelialized and whether reoperations are possible. Some members of the panel thought the patient brochure was too complicated, while others found it admirable. Several members expressed the need for labeling to indicate that device results for ASD patients may differ by age. The panel stressed the need to have on-site surgical back-up available and to have close collaboration between the echocardiographer and the interventional cardiologist.

FDA Questions to the Panel

1a. Please discuss whether individual endpoints, composite endpoints, or a combination of both should be used to evaluate the safety and effectiveness of the Amplatzer ASO device.

The panel thought that the 12-month composite success number was the most useful (which could include converted failures), but cautioned that all the endpoints had to be analyzed procedurally and that the presence of shunt and of complications must be noted separately as well. The panel stated that there are issues relative to age that must be given separately for safety and effectiveness to show that certain patients are at risk for complications, and that patients must understand that the result changes according to age and size of defect, with poorer results for older patients and larger defects.

1b) Are there sufficient data to support approval of the entire range of devices (4 mm to 38 mm) or a specific range of device sizes?

The panel did not favor restricting availability of different sizes of the device.

1c) Please discuss whether the data provided on ASD patients and the suggested analysis of the data from question 1a provide reasonable assurance of safety and effectiveness.

The panel thought the data adequate for assurance on safety. There was, however, discussion of assurance of effectiveness, with some members wanting more data on smaller or younger patients and longer follow-up.

2. Please discuss whether the data provided on fenestrated fontan patients and the suggested analysis of the data from question 1a provide reasonable assurance of safety and effectiveness.

The panel thought the data provided reasonable assurance of safety. The answer on efficacy was less evident, with some members wanting an aggressive analysis to look at size and age because of confounding variables on both sides.

3a. Please discuss any improvements that could be made to the training program.

The panel emphasized that careful case selection and explanation of technical aspects should be key parts of any training program.

3b. Please discuss training issues regarding placement of multiple devices in a single patient.

The panel recommended that this issue could be handled by use of proctored training.

4a. Please comment on the indications for use section as to whether it identifies the appropriate patient populations for treatment with this device.

The panel recommended specifying that ASD patients must have evidence of right ventricular volume overload and right ventricular symptoms and that the lack of data for dealing with certain subgroups should be clearly stated. Use or non-use with PFO patients should be clarified. Reanalysis of table 5 was recommended.

4b. Please comment on the contraindications section as to whether there are conditions under which the device should not be used because the risk of use clearly outweighs any possible benefit.

One panel recommendation was that labeling should state that candidates who are unable to have TEE or intracardial echocardiography should not have this device. Nickel allergy should also be discussed in the labeling, although there was no clear consensus that this should be a contraindication.

4c. Please comment on the warning precautions section as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

The panel recommended specifying the need for on-site surgical back-up and clarifying the instructions for use of coumadin.

4d. Please comment on the operator's instructions as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

The panel's comments were that the need for a proctor during training is essential, and the operator instructions should be revised.

4e. Please comment on the remainder of the device labeling as to whether it adequately describes how the device should be used.

Several members suggested that the patient brochure be amended and corrected. The panel recommended that data on results differing by age group should also be included.

5) Do you believe that additional follow-up data or postmarket studies are necessary to evaluate the chronic effects of the implantation of the Amplatzer device?

After discussing the possibility of a five-year registry, the panel recommended postmarket surveillance of higher-risk subgroups such as younger patients and those with larger defects.

Closing Sponsor and FDA Comments

Neither the sponsor representatives nor the FDA participants had additional comments.

Open Public Hearing

There were no requests to speak.

Recommendations and Vote

Megan Moynahan read the panel the voting instructions. A motion was made and seconded to recommend the PMA as approvable subject to the following conditions:

1) Sponsors should conduct postmarketing surveillance of high-risk subgroups such as those with larger size defects and those of younger age, with the mechanism of this surveillance to be determined by the FDA and sponsors together. This condition passed.
2) Labeling changes should be made to indicate which subgroups have and have not been studied, as discussed. Additional analysis of these data should be submitted to the FDA after eliminating the upper age ranges that were not included in the surgical group. The summary of data section should be expanded. This condition passed.

The motion to recommend the PMA as approvable subject to the above conditions was carried unanimously.

PMA P000049 NMT Medical's CardioSEAL Septal Occlusion System with Qwik Load

Dr. Tracy read the charge to the panel, which was to consider a septal occluder device for ventricular septal defects.

Open Public Hearing

There were no requests to address the panel.

Sponsor Presentation

John Ahern, President, CEO, and Chairman of NMT Medical, introduced the sponsor representatives and outlined the marketing history for the device, which has been commercially available in the United States under a humanitarian device exemption (HDE) and in Europe, with over 10,000 devices sold.

Carol Ryan, Vice President of Research and Development for NMT Medical, described the device, which is designed for percutaneous closure of intracardiac defects, its delivery system, and design features.

John E. Mayer, M.D., Boston Children's Hospital, described the location and occurrence of ventricular septal defects (VSDs) as seen at Boston Children's Hospital over a 14-year period. He discussed incremental risk factors after repair of VSDs, noting that multiple VSDs are associated with the highest mortality, and he defined a "high risk" VSD from the surgical viewpoint. Dr. Mayer summarized the current treatment and approaches for VSD, either through conventional surgery or a transcatheter approach.

Peter Laussen, MBBS, of Boston Children's Hospital, showed a video illustrating the technique of device use and the risk of adverse hemodynamic events, stressing that patients can be safely managed with appropriate anticipation and

collaboration between staff. These events are primarily related to the catheter pathway and are independent of other variables. He warned that acute resuscitation should be anticipated, but events are reversible and present a low risk of morbidity and mortality.

Kathy J. Jenkins, M.D., gave the clinical trial overview. She listed the data sets submitted, which were based on a pivotal cohort from the CardioSEAL high–risk study of 57 patients and other nonpivotal cohorts. The CardioSEAL high-risk study was a prospective, multicenter trial that included patients with VSDs and other types of defects. The study was designed to evaluate device safety and efficacy in patients with limited acceptable alternatives and used a prospective cohort of implanted patients without a control group. Patients were entered by an independent peer review team according to specified criteria, and outcome was evaluated at intervals by chest x-rays, EKG, echocardiogram, and fluoroscopy. Efficacy was assessed by a Clinical Status Scale by lesion using two ordinal scales and by patient using eight ordinal scales, as well as echo closure status. Efficacy was evaluated as a change from baseline at six months as shown by echo. Dr. Jenkins explained the two scales and the definitions of echo closure status. Safety was assessed according to a comprehensive definition of all adverse events occurring at any point, which were reviewed independently.

The nonpivotal Clamshell I follow-up study was also used for safety and efficacy assessment. This was a registry of all patients implanted at Children's during the trials with clamshell devices. Patients were followed to screen for device-related and major clinical events. Dr. Jenkins explained the recommended testing schedule and classification of adverse events. Safety was assessed by identification of device and fracture-related events only. Efficacy was based on echo closure status.

Kimberlee Gauvreau, ScD., Boston Children's Hospital, presented the trial results and analysis. She explained the efficacy endpoints and sample size calculations and presented patient enrollment data on the 107 devices (57 patients) implanted. She stated that there was successful defect closure and shunt reduction in 84% of patients by six months, and improved clinical status was observed in 72% of patients. While there was "more than small" residual flow in 94.0% of patients prior to implantation, only 9% had more than small flow at the six-month follow-up. Safety results revealed that 98.3% of patients with attempted implant experienced at least one adverse event through the most recent follow-up, with 37.9% of patients having at least one serious or moderately serious device or implantation-related event. Ms. Gauvreau listed these moderately serious or serious events by time of event and discussed the two ongoing device- or implant-related events. There were four deaths in the pivotal cohort and four device explants, as well as 17 device arm fractures in the pivotal cohort.

In the nonpivotal cohort of the Clamshell I registry, which included 87 patients and 140 devices, there were a total of 25 device-related adverse events, of which 18 were serious or moderately serious. Analysis of these events by time of event showed similar results to those in the pivotal cohort. Efficacy data on the nonpivotal cohort of 87 patients showed residual flow to be trivial or small in some 80% of patients at most recent follow-up. Additional information was not presented on the other non-pivotal cohorts.

Dr. Jenkins concluded that in patients at high risk for poor outcomes after surgery, VSD closure using the device resulted in successful defect closure and shunt reduction in over 80% of cases by six months after implantation. Device closure also resulted in improved clinical status in 72 % of patients. Device arm fractures were

observed in 16% of implanted devices, but no clinical consequences have been attributed to these fractures. Peri-procedure events occurred frequently, but most were successfully treated. However, one infant death was directly attributed to the procedure, and two patients have ongoing clinical impairment from moderately serious or serious device or implant related events, both with valve injuries. Late onset adverse events attributed to the device were not observed in the pivotal cohort.

FDA Presentation

Donna Buckley introduced the FDA review team and described the device. She also explained that an HDE is similar to a PMA application but exempt from effectiveness requirements because it is intended to benefit patients with diseases or conditions that affect fewer than 4,000 people. She noted that the CardioSEAL device was approved under an HDE for the same intended use as in the PMA application. Ms. Buckley reviewed the in vitro, biocompatibility, and in vivo testing, all of which demonstrated the integrity of the device for its intended use. She stated that there were no outstanding nonclinical testing issues.

John Stuhlmuller, M.D., presented the clinical evaluation, listing the five different clinical data sets but reviewing only the pivotal cohort for VSD closure. He explained that this cohort is a retrospectively derived patient subset of the high-risk registry, which is an open-label, single arm registry without a control group that is also primarily a single-center study. A total of 74 patients were identified for inclusion in this cohort; and devices were placed in 57 of 58 patients in which placement was attempted. Multiple devices were placed in 26 patients, and multiple procedures done in six patients.

Effectiveness was assessed using the Clinical Status Scale (CSS) at six months; safety was assessed by evaluation of adverse events. Dr. Stuhlmuller explained the CSS, in which a change of one in either direction represents a clinically meaningful change. Of the 57 implanted patients, 44 completed follow-up. A median change of two categories was demonstrated, and 84% of the procedures were considered successful.

Dr. Stuhlmuller explained that safety assessments were made at one, six, 12, and 24 months. Adverse events were characterized as device related (including arm fractures), implantation related, and catheterization related. Adverse events occurred in 57 out of 58 patients in which placement was attempted, with a total of 222 events noted. The majority of these (85) were catheterization related. Device arm fractures were noted in 34 of 107 devices.

Open Committee Discussion

David Skorton, M.D., the lead panel reviewer, noted that this was a difficult clinical problem with few easy answers because the decision to pursue surgery or device implantation was a leap of faith. He asked sponsors for additional clarification on the nonparametric rank test used in the CCS and also questioned why they sought conversion from an HDE to a PMA. Sponsors replied that it was to reduce the institutional burden on centers wishing to use the device in life-saving situations.

Panel members asked about the validation of the CSS scale with other scales and the relationship between subscales. There was some panel disagreement, with one member who thought the clinical data spoke for itself and the differences between scales irrelevant. Another disagreed, saying that the endpoint had been incorrectly defined and that the procedure could not be defined as successful if serious complications occurred.

There was considerable panel discussion about whether the results were center-dependent and how that center's experience could be transferred to less experienced institutions. Concern was expressed about the high rate of device fracture. One member recommended revised labeling to specify conditions or anatomical configurations where the device should not be used, such as patients not likely to do well with a catheterization procedure, VSDs in locations within five mm of the semilunar or AV valves or patients with valve apparatus too small to have 10 French valves. It was suggested that the illustrations be redone to show the complexity of the procedure. One member asked how physicians can be trained to get informed consent for a procedure with high odds of failure but good odds of results if the procedure succeeds. The need for a team approach in training was emphasized.

FDA Questions to the Panel

1a. Based on the information provided, please discuss the description "complex VSD" as the defining indication for use of the CardioSEAL for VSD closure.

The panel referred to Dr. Mayer's definition of a high risk VSD (low probability of satisfactory surgical exposure without compromising ventricular function and high probability of significant residual VSD) as sufficient, but added that post-infarction VSD should be contraindicated.

1b. In the absence of a control group, please discuss how to evaluate the safety and effectiveness of the CardioSEAL device.

The panel thought there had been sufficient discussion of this point already and noted that the group "is what it is—a very high risk group."

2. Does the use of the Clinical Status Scale allow for a clinically meaningful assessment of effectiveness for the device?

As noted above, panel members disagreed on this point. Some found the CSS to be a useful source of data. One argued, however, that there should have been a composite endpoint combining efficacy results with complication rates, while other members thought no such composite was possible.

3. Based on the data provided and your comments regarding questions 1 and 2, please discuss whether these data provide reasonable assurance of safety and effectiveness.

Again, members of the panel were split on this issue, with one arguing that the device should remain under an HDE because efficacy had not been adequately demonstrated for PMA approval. The rest of the panel thought that within this small study group there was adequate assurance of efficacy as well as safety.

4a. Please discuss any improvements that could be made to the training program.

The panel wished to emphasize the seriousness of this surgery and the need to ensure that training should include proctored operations with a group training approach. The panel urged rigorous training that the FDA would develop in conjunction with the sponsor.

4b. More than one device was placed in 26 patients. Please discuss training issues regarding the placement of multiple devices in a single patient.

Again, the panel stressed the need for team training, noting that the placement of multiple devices means a more complex surgery requiring greater training and team cooperation.

5a. Please comment on the indications for use section as to whether it identifies the appropriate patient populations for treatment with this device.

The panel had no further comments.

5b. Please comment on the contraindications section as to whether there are conditions under which the device should not be used because the risk of use clearly outweighs any possible benefit.

The panel added as contraindications a clot in the left atrium and any position that would interfere with the functioning of any valve.

5c. Please comment on the warnings/precautions section as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

In addition to the anatomical caveats noted in the discussion, the panel added a warning that posterior muscular defects present a higher risk.

5d. Please comment on the operator's instructions as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

More and better illustrations were recommended, as was proctored training.

5e. Please comment on the remainder of the device labeling.

The panel had no additional comments.

6. Based on the clinical data provided in the panel package, do you believe that additional follow-up data or postmarket studies are necessary to evaluate the chronic effects of the implantation of the CardioSEAL device? If so, how long should patients be followed and what endpoints and adverse events should be measured?

The panel found it difficult to recommend something based on a set of patients so small and so ill. One suggestion was to look at patient outcome and efficacy by center.

Closing Sponsor or FDA Remarks

Neither the sponsor representatives nor the FDA team had additional remarks.

Open Public Hearing

There were no requests to speak.

Panel Recommendations and Vote

Megan Moynahan read the panel voting instructions. A motion was made and seconded to recommend the PMA as approvable subject to the following conditions:

1) Mandatory postmarket studies would be conducted to look at each patient with annual fluoroscope and echocardiography or some other diagnostic method for six endpoints: the status of the device arm; device thrombosis, global and right ventricular function; endocarditis; evidence of ventricular arrhythmia or disturbance; and evidence of residual shunt. This condition passed unanimously.

2) Augmented training procedures would be developed by the FDA and the sponsors. This condition passed unanimously.

3) Labeling clarifications would be made as recommended above and verified. This condition passed unanimously.

The motion to recommend the PMA as approvable subject to the above conditions passed by a vote of nine to one. The member who voted against the motion stated that he did so because he thought the efficacy endpoint was unsatisfactory, as was the safety record. Other members stated that they voted to recommend the PMA as approvable because of the desperate need to make this device more easily available.

Mr. Dillard and **Panel Chair Dr. Tracy** thanked the sponsors and the panel members for their work. Dr. Tracy adjourned the session for the day at 6:03 p.m.

OPEN SESSION—September 11, 2001

Warren K. Laskey, M.D., Acting Chairperson, called the session to order at 8:05 a.m. and read the charge to the panel, which was to consider a PMA for a surgical adhesive. **Executive Secretary Megan Moynahan** read the conflict of interest statement, noting that a waiver had been granted to Janet Wittes, Ph.D., for her interest in firms potentially affected by the day's deliberations. She also read an appointment to voting status for Michael D. Crittenden, M.D., and Thomas B. Ferguson, M.D., as well as an appointment as acting chairperson for Dr. Laskey. **Dr. Laskey** asked the panel members to introduce themselves and note their areas of expertise.

Open Public Hearing

There were no requests to speak from the audience. **James E. Dillard, Director of the Division of Cardiovascular and Respiratory Devices,** presented a plaque and letter of appreciation to outgoing panel member **Dr. Crittenden** for his service to the panel.

Sponsor Presentation—P01003 for CryoLife, Inc.'s BioGlue Surgical Adhesive

James C. Vander Wyk, Ph.D., Vice President for Regulatory Affairs and Quality Assurance for CryoLife, Inc., introduced the sponsor team and summarized the regulatory history of the device, which began as an investigational device exemption (IDE) for acute aortic dissection repair in 1998 and was approved under an HDE in 1999. Sponsors were seeking PMA approval for use as an adjunct to standard methods of cardiac and vascular repair such as sutures or staples to provide hemostasis. The device is commercially available overseas, and no reports of adverse events have been filed. Dr.

Vander Wyk described the device and its delivery system as well as its mechanism of action and showed a video of its application.

David M. Fronk, M.S., Vice President for Clinical Research of CryoLife, Inc. discussed nonclinical performance. He presented results of in vitro shear strength comparisons, biocompatibility testing, in vivo animal evaluations, histopathology of BioGlue implants, and immunology testing, focusing primarily on immunotoxicity testing results. Immunotoxicity testing showed a low risk of anaphylactic reaction by the repeated use or long-term exposure of BioGlue. However, once a patient is sensitive, other medical devices or medicines containing BSA theoretically may induce an anaphylactic reaction. Therefore, sponsors recommended a contraindication for those sensitive to bovine serum.

Joseph S. Coselli, M.D., presented the results of the clinical trial, which was a multicenter trial seeking to demonstrate a decrease in the frequency of intraoperative anastomotic site bleeding in patients receiving the device as an anastomotic prophylactic sealant as compared to patients receiving standard surgical anastomotic repair. He listed the primary and secondary effectiveness endpoints and explained the study design and sample size determination. After explaining inclusion and exclusion criteria, Dr. Coselli looked at the patient characteristics of the 76 device and 75 control patients, noting that the groups were very similar to each other and quite diverse within each group by age, gender, and race. Primary effectiveness results significantly favored the device group both by patient and by anastomosis. Secondary endpoints involving intra-operative and postoperative blood products showed the treatment group and control to be essentially identical. The secondary endpoint of additional hemostatic measures showed the use of

pledgets for primary anastomosis to be lower for the device. Analysis of reoperations and mortality showed no significant difference, as did an analysis of procedural complications, although there was a reduction in neurological deficits in the device group. Product-related complications included one application to non-target tissue and one failure to adhere, both of which were included in the user information. Dr. Coselli concluded that BioGlue is more effective in achieving immediate anastomotic hemostasis when compared to standard repair and is as safe as standard repair. It also decreases the need for pledgeted sutures to reinforce the vascular tissue.

Joseph E. Bavaria, M.D., gave a clinician's view based on device use during a clinical trial at the University of Pennsylvania of 43 test and control subjects. He presented case histories of five patients, one with distal aortic repair, one with abdominal aortic aneurysm repair, one with aortic arch repair, one with ascending aortic repair, and one with acute type A dissection repair, all of whom benefited from device use.

FDA Presentation

Lisa Kennell, lead FDA reviewer, listed the FDA review team members and presented the regulatory history of BioGlue, a summary of the clinical study, and an overview of the nonclinical testing issues. She explained that BioGlue was first submitted under an Investigational Device Exemption (IDE) as an adjunct to Type A (ascending) aortic dissection repair. After IDE approval, the sponsor proposed applying for an HDE for both Type A and Type B dissections. After HDE approval, the sponsors began to have protocol deviations in randomization, consent, and off-label use. The FDA encouraged modification of the protocol to capture off-label uses in the ultimate labeling indications. This prompted the cardiac and vascular study arm. The proposed indication is for device

adjunctive use with standard methods of cardiac and vascular repair such as sutures or staples to provide hemostasis.

Ms. Kennell stated that the clinical study randomized patients to device group or control group of standard surgical hemostasis methods, with the goal of showing a 10% improvement in hemostasis with the device. Each group had about 75 patients. Ms. Kennell listed entrance criteria and the surgery locations. The primary endpoint was anastomotic hemostasis, with no need for additional agents to control bleeding at any point. Secondary endpoints were exposure to donor blood products, additional hemostatic agents, reoperation for bleeding, major and minor adverse events, and mortality. Ms. Kennell summarized that the study met its primary endpoint but showed no improvement in the device group on secondary endpoints, except in the reduced use of pledgets. The only significantly different safety result was a lower rate of neurological deficits in the device group.

On nonclinical testing, Ms. Kennell noted that the methods were acceptable and covered all important issues. However, the FDA expressed concern about immunogenicity findings from tests sponsors ran and asked FDA consultant **Henry Homburger, M.D.,** of the Mayo Clinic to comment. He concluded that the data were not sufficient to reach a firm conclusion about an immunologic response. Dr. Homburger recommended that it would be difficult to design additional animal studies to evaluate the human risk, so product labeling should include warnings regarding use in patients who are sensitive to bovine products and those with a prior history of immune-mediated diseases. He also recommended a warning about repeated use and a postmarket clinical

and in vitro study to assess production. **Ms. Kennell** then read the questions for panel discussion.

Open Committee Discussion

Salim Aziz, M.D., gave the lead panel review, in which he noted that animal findings do not necessarily translate into human antibody results. He raised a number of questions about use with various indications such as spiraling tears, use with traumatic aortic tears, atrial tears. He recommended that intravascular use be avoided and that precautions be taken to prevent BioGlue getting onto the valve itself.

Other panel questions involved use in an infected or wet field, effect if the substance gets into the bloodstream, effect on nerves, and use with Dacron or other grafts. Several members congratulated the sponsors on achieving excellent results and presenting them clearly. Statistical issues raised included whether the analysis of anastomosis was done correctly and whether each could be analyzed as an individual site. Concern about a long-term allergic reaction to bovine protein was also expressed.

FDA Questions for Panel Review

1.Please discuss the clinical implications of the primary and secondary endpoint data. The consensus of the panel was that the clinical results on the primary endpoint were outstanding. The secondary data were hard to address because the primary endpoint results were so stellar that there could have been some investigator bias. The panel would have liked to have seen more hemostasis analysis.

2. Please comment on whether there is adequate information to support the statement that "Our clinical investigators believe that the routine use of BioGlue in these patients

will allow them to modify their blood management protocol and should minimize the potentially life-threatening complication of postoperative hemorrhage."

The panel thought this to be an overstatement based on anecdotal evidence.

3.Please discuss whether the information supports reasonable assurance of safety and effectiveness of the BioGlue.

The panel consensus was that the information presented does support reasonable assurance of safety and effectiveness, at least in the short term.

4a. Should patients be advised of specific adverse events to be aware of that may suggest they are experiencing a sensitization reaction from the BioGlue?

The panel thought these events were likely to be extremely infrequent. They recommended advising and cautioning the user without mentioning any numbers or frequency. The use of nonbovine heparin could be suggested, if available.

4b) Please discuss whether sensitization has been adequately addressed with the clinical data as supplied. Are additional postapproval studies needed to assess the immune potential of BioGlue?

The panel thought that sensitization had been adequately addressed and that postapproval studies were not needed.

5) Please comment on the indications for use section as to whether it identifies the appropriate patient population for treatment with this device.

The panel thought this section was sufficient as written.

6) Please comment on the directions for use as to whether they adequately describe how the device should be used to maximize benefits and minimize adverse events.

The panel thought these directions were adequate, but suggested adding the word "unpressurized."

7) Do you have any other recommendations regarding the labeling of this device?

A reanalysis of the data in Tables 5 and 6 was recommended but not as a condition of approval.

Open Public Hearing

There were no requests to speak.

Recommendations and Voting

Mr. Dillard read the voting instructions to the panel. A motion was made and seconded to recommend the PMA as approvable, subject to the following condition: The labeling claim referring to minimizing the potentially life-threatening complication of postoperative hemorrhage should be deleted. This condition unanimously passed, as did the motion to recommend the PMA as approvable with conditions. The panel members stated that they voted in favor of the PMA because of the convincing safety and efficacy results.

Dr. Laskey thanked the remaining panel members and adjourned the session.

I certify that I attended the Open Session of the Circulatory Systems Devices Panel Meeting on September 10, 2001, and that this summary accurately reflects what transpired.

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Megan Moynahan, M.S.
Panel Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

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Cynthia Tracy, M.D.
Panel Chair, September 10, 2001

I approve the minutes of this meeting as recorded in this summary.

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Warren Laskey, M.D.
Acting Panel Chair, September 11, 2001

Summary minutes prepared by
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